CHRONIC TOXICITY SUMMARY

METHYLENE CHLORIDE

(dichloromethane, methylene dichloride)

CAS Registry Number: 75-09-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**400 µg/m^3 (100 ppb)**
Critical effect(s)	Carboxyhemoglobin formation above 2% in human workers
Hazard index target(s)	Cardiovascular system; nervous system

II. Physical and Chemical Properties (HSDB, 1999, except as noted)

Description	Colorless liquid
Molecular formula	CH_2Cl_2
Molecular weight	84.93
Density	1.32 g/cm^3 @ 20° C (ACGIH, 1991)
Boiling point	39.75° C
Vapor pressure	400 torr @ 24.1° C
Solubility	Miscible with most organic solvents, slightly soluble in water (ACGIH, 1991)
Conversion factor	1 ppm = 3.47 mg/m^3 @ 25° C

III. Major Uses and Sources

Methylene chloride (MC) is used in paint and varnish remover, in aerosols as a cosolvent or vapor pressure depressant, and in solvent degreasing and metal cleaning. It is also used in plastics processing and in extraction of fats and oils from food products (HSDB, 1999). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California, based on the most recent inventory, were estimated to be 3,504,271 pounds of methylene chloride (CARB, 1999a). Both mean and maximum monitored ambient methylene chloride concentrations have decreased slightly between 1990 and 1996 (CARB, 1999b). Median and maximum concentrations were 1.09 and 11 ppb in 1990 and 0.66 and 5.6 ppb in 1996.

IV. Effects of Human Exposure

Effects of a controlled 2-hour inhalation exposure to MC included CNS depression at concentrations of 1000 ppm (3500 mg/m^3) or more and increased blood carboxyhemoglobin (COHb) content at lower concentrations (500 ppm) due to metabolism of MC to carbon monoxide (Stewart *et al.*, 1972). High levels of COHb can be found in the blood hours after exposure to methylene chloride, due to its partitioning into fat and its slow release into circulation with subsequent metabolism, leading to formation of carbon monoxide (Engstrom and Bjurstrom, 1977). In situations of chronic exposure, carbon monoxide toxicity is also of concern. Barrowcliff (1978) documented the case of an adult male who developed an unsteady gait, a peculiar dysarthria and a loss of memory. The man had worked with 15-50 liters of methylene chloride daily for 3 years in a poorly ventilated room while cleansing road materials. No natural disease could be found to explain his conditions and the effects were attributed to chronic carbon monoxide poisoning.

Twelve women volunteer subjects were exposed to 0, 300, or 800 ppm methylene chloride for 4 hours (Fodor and Winneke, 1971). Neurobehavioral vigilance was measured by auditory discrimination of intensity of certain sound pulses against a background of continuous white noise. A significant interactive effect between methylene chloride concentration and duration of exposure using 2-way ANOVA ($p < 0.01$) was found.

Human erythrocytes enzymatically convert methylene chloride to formaldehyde in cell-culture experiments (Hallier *et al.*, 1994).

A subacute controlled exposure of eleven resting non-smokers to methylene chloride was conducted by DiVincenzo and Kaplan (1981a). The eleven subjects were exposed to 50, 100, 150, or 200 ppm methylene chloride for 7.5 hours on 5 consecutive days. Exposure to all concentrations led to dose-dependent elevation in COHb concentrations in the blood and elevated exhaled CO. The peak blood COHb saturations were 1.9, 3.4, 5.3, and 6.8%, respectively, for the 50, 100, 150, and 200 ppm groups.

Divencenzo and Kaplan (1981a) also measured COHb percentage in the blood of workers occupationally exposed to methylene chloride and a group of workers not exposed to methylene chloride. The 19 workers exposed to methylene chloride had mean blood COHb concentrations of 2.3% in the morning and 3.9% at the end of the work-shift. Ambient concentrations in the workplace were estimated from 57 samples, which ranged from 0 to 250 ppm, with a mean concentration of 40 ppm. Three exposed workers also wore monitors to estimate personal exposures. The time-weighted average exposure for these workers was 33 ppm. Controls (8 subjects) had significantly lower mean blood COHb concentrations of 0.8% in the AM and 1.3% in the PM compared with the exposed workers. The length of employment of the exposed workers was not given.

A companion study by DiVincenzo and Kaplan (1981b) showed that smoking and methylene chloride exposure result in an additive effect on COHb levels compared with levels in non-smokers. Similarly, light, moderate or heavy exercise workloads resulted in higher COHb levels.

Soden *et al.* (1996) showed a dose-response increase in carboxyhemoglobin levels in non-smokers with increasing methylene chloride exposure in workers involved in triacetate fiber production. Carboxyhemoglobin levels ranged from 1.77% to 4% from exposures ranging from 6.5 to 89.7 ppm, respectively. The number of employees in the study was not reported.

Although animal studies have shown COHb-induced cardiovascular effects following MC exposure (Aviado *et al.*, 1977), no data exist on this outcome in humans. However, studies of men with coronary artery disease and exercise-induced angina report a decrease in time to onset of exercise-induced angina following exposure to carbon monoxide (CO) at concentrations sufficient to result in blood COHb levels of about 2% (Kleinman *et al.*, 1989; Allred *et al.*, 1989). A physiologically based pharmacokinetic model of MC and CO estimated that a 1-hour exposure to 340 ppm (1200 mg/m^3) MC at a ventilation rate of 9 liters/min would result in a peak blood COHb level of 2% (Andersen *et al.*, 1991; Reitz, 1994). The California Ambient Air Quality Standard for CO is based on a blood COHb level of 2% (CARB, 1982).

An epidemiological study of 751 male workers in the Eastman Kodak Company exposed to daily 8-hour time-weighted average concentrations of 30-125 ppm methylene chloride for up to 30 years was conducted by Friedlander and associates (1978). A control group of workers in production but not exposed to methylene chloride was used together with New York state cause and age-specific mortality rates. The follow-up period for these workers was 13 years, with 97% success. The studies did not indicate any increase in risk of death from circulatory disease, cancer, or other causes due to methylene chloride exposure.

A study of female pharmaceutical workers in eight different factories exposed to a variety of organic solvents indicated that solvent exposure, and particularly methylene chloride exposure, resulted in an increase in spontaneous abortions (Taskinen *et al.*, 1986). In all, 1795 pregnancies were followed, with 142 spontaneous abortions occurring. The odds ratio for methylene chloride exposure was 1.0 to 5.7 (average = 2.3; $p < 0.06$). There was a significant effect of exposure to 4 or more solvents, compared with age-matched controls ($p < 0.05$). The concentrations of MC were not reported in the study.

The U.S. Occupational Safety and Health Administration reduced its permissible exposure limits (PEL) for MC from 500 ppm to 25 ppm in 1997 (U.S. CFR, 1997).

V. Effects of Animal Exposure

Nitschke *et al.* (1988) found that a 2-year exposure to 0, 50, 200, or 500 ppm MC for 6 hours/day, 5 days/week resulted in significant histopathologic lesions in the livers of rats exposed to 500 ppm. No significant adverse effects were observed at 200 ppm or lower. The predominant hepatocellular lesion was fatty vacuolization of hepatocytes.

Female B6C3F1 mice inhaling 2000 ppm MC for 1 to 26 weeks had 40 to 60% lower cell turnover rates of bronchiolar cells compared with controls (Kanno *et al.*, 1993). At this concentration no observable pathological changes were found in the lungs of MC exposed animals.

A continuous exposure of mice (16 per group) to 100 ppm MC for 1, 2, 3, 4 or 10 weeks resulted in signifcant elevation in liver triglycerides beginning at 2 weeks and lasting throughout the 10-week period (Weinstein and Diamond, 1972). Liver/body weight ratios were unaffected at any time point. After 1 week, small fat droplets were apparent in centrilobular hepatocytes and a decrease in hepatic glycogen was also noted. Necrosis was not observed during the 10-week period, but fat droplet size increased and glycogen depletion persisted.

Male and female Sprague-Dawley rats and Golden Syrian hamsters inhaled methylene chloride (0, 500, 1500, or 3500 ppm) for 6 hr per day, 5 days a week over 2 years (Burek *et al.*, 1984). The groups consisted of 129 rats per sex per concentration, and 107 to 109 hamsters per sex per concentration. Females rats inhaling 3500 ppm had an increased mortality rate while female hamsters inhaling 1500 or 3500 ppm had decreased mortality rates. Slight histopathological findings were noted in livers of rats exposed to 500, 1500, or 3500 ppm MC. Decreased amyloidosis was also found in livers and other organs of hamsters at each of the three MC concentrations. Overall, effects were more potent in rats compared with hamsters, which had fewer spontaneous age-related changes, decreased mortality (at least for females), and evidence of specific target organ toxicity was weak. Carboxyhemoglobin values were elevated in both rats and hamsters exposed to 500 ppm or more of MC, with the percentage increase greater in hamsters than in rats.
Monkeys were observed to be more susceptible subjects for methylene chloride induced COHb than dogs upon 14-week subchronic continuous exposure to 25 or 100 ppm (Haun *et al.*, 1972). At 25 ppm, approximately 1.5% COHb was reached in the 4 monkeys, compared to approximately 0.5% in 16 dogs. Monkeys exposed to 100 ppm MC had COHb levels of approximately 4% compared with 2% in the dogs.

Oral ethanol pretreatment in rats has been shown to suppress the COHb formation characteristic of methylene chloride exposure through inhibition of biotransformation of methylene chloride (Glatzel *et al.*, 1987).

Gerbils (10/sex per group; 60 controls) exposed continuously to MC concentrations of 210, 350, or 700 ppm for a period of 3 months, with a 4-month follow-up period, showed irreversible cellular and biochemical changes in brain (Rosengren *et al.*, 1986). A high mortality rate (19/20) was observed in the 700 ppm group, and this exposure was terminated after 7 weeks. The gerbils exposed to 350 ppm also had a high mortality rate (9/20) and this exposure was terminated after 10 weeks. The gerbils exposed to 210 ppm had no premature mortality and the exposure continued for the full 3 months. Four months after termination of exposure, the animals in the 350 and 210 ppm groups had significantly decreased brain DNA content in the hippocampus. The 350 ppm group exhibited elevated astroglial proteins in the frontal and sensory motor cerebral cortex, consistent with astrogliosis in these regions. In addition, the gerbils exposed to 350 ppm MC had significantly decreased DNA in the cerebellar hemispheres. Complimentary studies by these investigators showed that the formation of carboxyhemoglobin did not increase in gerbils between the 210 and 350 ppm exposures, indicating that the metabolism of MC to CO is saturable at concentrations below those in the study. On the other hand, the neurotoxic brain biochemical alterations were significantly greater in gerbils exposed to 350 ppm as compared

with the 210 ppm group, implying that carboxyhemoglobin induced cerebral hypoxia is not the major cause of MC-induced neurotoxicity in the brain.

Rats (50 per sex per group) were exposed to 0, 1000, 2000, or 4000 ppm methylene chloride 6 hours/day, 5 days/week for 102 weeks (NTP, 1986). Both sexes exhibited hemosiderin pigmentation in the liver in a dose-dependent fashion, beginning with the 1000 ppm concentration. Squamous metaplasia of the nasal cavity was observed in female rats, and thyroid C-cell hyperplasia was observed in males exposed to 2000 ppm or greater. Kidney tubule degeneration (not otherwise specified) was increased at all exposure levels.

Mice (50 per sex per group) exposed to 0, 2000, or 4000 ppm methylene chloride 6 hours/day, 5 days/week for 102 weeks showed increased incidence of liver cytologic degeneration and splenic atrophy at 4000 ppm (males) (NTP, 1986). Male and female mice also had an increased incidence of kidney tubule casts (not otherwise specified) at 2000 ppm or greater, and significant testicular atrophy was observed in males at 4000 ppm. Female mice showed cytologic degeneration in the liver at 2000 ppm or greater, and ovarian atrophy at 2000 ppm or greater.

A six month exposure to 5000 ppm MC of 8 guinea pigs for 7 hours/day, 5 days/week resulted in 3 deaths; 2 showed moderate centrilobular fatty degeneration of the liver and extensive pneumonia at necropsy (Heppel *et al.*, 1944). None of the 14 control animals died. Food consumption and body weight were lower in the exposed guinea pigs, compared with control pigs. One out of 12 rats died at this concentration, and the liver histology in this animal revealed multiple thrombi in renal vessels, associated with marked cortical infarction. By comparison, dogs and rabbits showed no signs of illness, nor were blood pressure or hematological values altered at the 5000 ppm concentration. At 10,000 ppm, 2 of 4 dogs showed moderate centrilobular congestion, narrowing of liver cell cords, and slight to moderate fatty degeneration. One of 2 monkeys revealed disseminated tuberculosis lesions, but no other histological alterations. Four out of 6 guinea pigs had moderate fatty degeneration of the liver at this concentration.

The offspring of rats (10 dams per group) exposed during gestation to 0 or 4500 ppm methylene chloride exhibited altered rates of behavioral habituation to novel environments (Bornschein *et al.*, 1980). This effect was observed beginning at 10 days of age but was still demonstrable in rats 150 days old. The authors concluded that elevated maternal COHb could have been a contributing factor in the developmental impairment.

In a study of the effects of methylene chloride on estrous cycle and serum prolactin, groups of 15 female rats were exposed to 0 or 3500 ppm for 6 hours/day for 15 to 19 consecutive days (Breslin and Landry, 1986). Males (15 per group) were exposed for 5 hours/day for 5 consecutive days. Female rats exhibited decreased body weight and increases in the estrous cycle duration and in serum prolactin. Males did not show any significant effects on serum prolactin from methylene chloride exposure.

Pregnant mice and rats were exposed to 0 or 1250 ppm MC 7 hours/day, on days 6 through 15 of gestation (Schwetz *et al.*, 1975). Significantly elevated absolute liver weights were seen in

maternal animals from both species. In addition, significantly increased incidences of delayed ossification of the sternebrae were seen in both species, compared to controls.

Methylene chloride exposure of female rats before or during gestation to 4500 ppm resulted in elevated maternal liver weights and decreased birth weights of the offspring, but no terata or skeletal/soft tissue anomalies (Hardin and Manson, 1980).

A 2-generation reproduction test was conducted by Dow Chemical Company (Nitschke *et al.*, 1985) which showed no significant reproductive or developmental effects in rats exposed to 0, 100, 500, or 1500 ppm MC 6 hours/day, 5 days/week, for 14 weeks. The exposure conditions were identical for the F_0 and F_1 generations.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	DiVincenzo and Kaplan (1981a)
Study population	19 workers, 8 controls
Exposure method	Occupational inhalation exposure
Critical effects	Significantly elevated carboxyhemoglobin levels (> 2%)
LOAEL	40 ppm (ambient workplace exposures averaged 40 ppm with a range of 0 to 250 ppm); controls = 0 ppm
NOAEL	Not observed
Exposure continuity	8 hours/day, 5 days/week
Exposure duration	Length of employment unspecified
Average occcupational exposure	14 ppm for LOAEL group (40 x 10/20 x 5/7)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	1 (see following text for explanation)
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.1 ppm (100 pbb; 0.4 mg/m^3; 400 µg/m^3)

Workers were exposed to average measured concentrations of 40 ppm during the workday, and the personal monitors on 3 of the subjects indicated a 8-hour time-weighted average of 33 ppm over a 2-week period. The average COHb levels were 3.9% at the end of the work-shift. Elevated carboxyhemoglobin concentrations of above 2% are considered to aggravate angina in some individuals (CARB, 1982). In effect, 2% COHb can be considered a NOAEL for aggravation of angina. Therefore, the 33 ppm concentration was considered a LOAEL for the formation of greater than 2% COHb. The duration of the employment period was not specified. However, in the DiVincenzo and Kaplan (1981a) study, the levels of COHb did not appear to increase over a period of 5 days in experimental exposures using volunteers, therefore an uncertainty factor for subchronic exposure was not necessary. A number of factors contribute to

the uncertainty in determining the degree of sensitivity to methylene chloride, including activity level, metabolic enzyme activity, age, and background COHb status (e.g., from smoking, etc.).

The subchronic study by Haun *et al.* (1972) with monkeys reported a NOAEL of 25 ppm and a LOAEL of 100 ppm for 2% COHb formation following a 14-week exposure. These results are consistent with the LOAEL reported in the DiVincenzo and Kaplan study. However, the human occupational study likely contains less uncertainty, since the toxicokinetics of the effect, including rate of formation of CO and thus COHb is metabolism-dependent, resulting in considerable potential interspecies differences.

The study in hamsters by Burek *et al.*(1984) showed a LOAEL for elevated carboxyhemoglobin of 500 ppm. A time-weight average exposure and HEC of 89 ppm was calculated. Using a 10-fold LOAEL uncertainty factor, a 3-fold interspecies uncertainty factor for residual uncertainty not accounted for in the HEC calculation, and a 10-fold intraspecies uncertainty factor, a REL of 300 ppb or 1000 $\mu g/m^3$ was derived. Thus, the REL derived from the best available animal study is comparable to the 400 $\mu g/m^3$ REL derived from the best-available human study.

VII. Data Strengths and Limitations for Development of the REL

The major strength of the key study (DiVincenzo and Kaplan, 1981a) used to derive the REL for methylene chloride is that human health effects were observed. The major uncertainties from the key study itself are the lack of a NOAEL observation, the difficulty in estimating exposures, and the discontinuous and variable nature of the exposures.

The health effects database for methylene chloride includes, in addition to an adequate study of human occupational exposures (DiVincenzo and Kaplan, 1981a), an adequate lifetime inhalation exposure study in 2 species of laboratory animals (Burek *et al*., 1984). The REL values derived from these studies (400 $\mu g/m^3$ vs. 1,000 $\mu g/m^3$) are comparable. That both the human and animal studies measured the same endpoint and arrived at similar conclusions is a circumstance that is rarely found but one that considerably increases the weight of evidence from which the REL was derived. The two studies complement each other, as the animal study involved controlled, measured exposures over a lifetime but introduces the uncertainty of predicting human health effects from animal observations, and the human study involved poorly characterized human exposures but lacks the uncertainty inherent in interspecies extrapolation.

VIII. References

Allred EN, Bleecker ER, Chaitman BR, Dahms TE, Gottlieb SO, Hackney JD, Hayes D, Pagano M, Selvester RH, Walden SM, and Warren J. 1989. Acute effects of carbon monoxide exposure on individuals with coronary artery disease. Health Effects Research Institute (HEI) Research Report No. 25., Cambridge, MA: HEI.

ACGIH. 1991. American Conference of Governmental Industrial Hygienists. Documentation of Threshold Limit Values and Biological Exposure Indices. 6th edition Cincinnati, OH: ACGIH.

Andersen ME, Clewell HJ III, Gargas ML, MacNaughton MG, Reitz RH, Nolan RJ, and McKenna MJ. 1991. Physiologically based pharmacokinetic modeling with dichloromethane, its metabolite, carbon monoxide, and blood carboxyhemoglobin in rats and humans. Toxicol. Appl. Pharmacol. 108:14-27.

Aviado DM, Zakhari S, Watanabe T. 1977. Methylene chloride. In: Golberg L. (ed.) Non-Fluorinated Propellants and Solvents for Aerosols, Cleveland, OH: CRC Press, pp.19-45.

Barrowcliff DF. 1978. Chronic carbon monoxide poisoning caused by methylene chloride paintstripper. Med. Sci. Law 18(4):238.

Bornschein RL, Hastings L, and Manson JM. 1980. Behavioral toxicity in the offspring of rats following maternal exposure to dichloromethane. Toxicol. Appl. Pharmacol. 52:29-37.

Breslin WJ, and Landry TD. 1986. Methylene chloride: Effects on estrous cycling and serum prolactin in Sprague-Dawley rats. Unpublished study by Dow Chemical U.S.A., Midland, MI 48674.

Burek JD, Nitschke KD, Bell TJ, Wackerle DL, Childs RC, Beyer JE, Dittenber DA, Rampy LW, and McKenna MJ. 1984. Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters. Fundam. Appl. Toxicol. 4:30-47.

CARB (California Air Resources Board). 1982. California Air Resources Board. California Ambient Air Quality Standards for Carbon Monoxide (Sea Level). Technical Support Document. Sacramento, CA: California Air Resources Board, Technical Support Division.

CARB (California Air Resources Board). 1999a. Air toxics emissions data collected in the Air Toxics Hot Spots Program CEIDARS Database as of January 29, 1999.

CARB (California Air Resources Board). 1999b. 1990-1996 Statewide Methylene Chloride Summary, ppb. WWW document (http://www.arb.ca.gov/aqd/dcm/dmstate.htm).

DiVincenzo GD, and Kaplan CJ. 1981a. Uptake, metabolism, and elimination of methylene chloride vapor by humans. Toxicol. Appl. Pharmacol. 59:130-140.

DiVincenzo GD, and Kaplan CJ. 1981b. Effect of exercise or smoking on the uptake, metabolism, and excretion of methylene chloride vapor. Toxicol. Appl. Pharmacol. 59:141-148.

Engstrom J, and Bjurstrom R. 1977. Exposure to methylene chloride: content in subcutaneous adipose tissue. Scand. J. Work Environ. Health 3:215-224.

Fodor GG, and Winneke H. 1971. Nervous system disturbances in men and animals experimentally exposed to industrial solvent vapors. Proc. 2nd Intl. Clean Air Congr. New York: Academic Press. pp. 238-243.

Friedlander BR, Hearne T, and Hall S. 1978. Epidemiologic investigation of employees chronically exposed to methylene chloride. J. Occup. Med. 20:657-666.

Glatzel W, Tietze K, Gutewort R, and Pankow D. 1987. Interaction of dichloromethane and ethanol in rats: Toxicokinetics and nerve conduction velocity. Alcohol. Clin. Exp. Res. 11(5):450-452.

Hallier E, Schroder KR, Asmuth K, Dommermuth A, Aust B, Goerens HW. 1994. Metabolism of dichloromethane (methylene chloride) to formaldehyde in human erythrocytes: influence of polymorphism of glutathione transferase theta (GST T1-1). Arch. Toxicol. 68:423-427.

Hardin BD, and Manson JM. 1980. Absence of dichloromethane teratogenicity with inhalation exposure in rats.Toxicol Appl Pharmacol 1980 52(1):22-28.

Haun CC, Vernot EH, and Darmer KI. 1972. Continuous animal exposure to low levels of dichloromethane. Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Dayton, OH. AMRL-TR-72-130.

HSDB. 1999. Hazardous Substance Data Bank. National Library of Medicine, Bethesda, Maryland. WWW database (http://sis.nlm.nih.gov/sis1/).

Heppel LA, Neal PA, Perrin TL, Orr ML, and Porterfield VT. 1944. Toxicology of dichloromethane (methylene chloride). I. Studies on effects of daily inhalation. J. Ind. Hyg. Toxicol. 26(1):8-16.

Kanno J, Foley JF, Kari F, Anderson MW, Maronpot RR. 1993. Effect of methylene chloride inhalation on replicative DNA synthesis in the lungs of female B6C3F1 mice. Environ Health Perspect 101 Suppl 5:271-276.

Kleinman MT, Davidson DM, Vandigraff RB, Caiozzo VJ, and Whittenberger JL. 1989. Effects of short-term exposure to carbon monoxide in subjects with coronary artery disease. Arch. Env. Health 44(6):361-369.

NTP. 1986. National Toxicology Program. Toxicology and carcinogenesis studies of dichloromethane (methylene chloride) in F344/N rats and B6C3F1 mice. NIH Publication 86-2562. Reasearch Triangle Park, NC: U.S. Dept. of Health and Human Services.

Nitschke KD, Eisenbrandt DL, and Lomax LG. 1985. Methylene chloride: Two -generation reproduction study in Fischer 344 rats. Midland, MI: Dow Chemical Company. February 5.

Nitschke KD, Burek JD, Bell TJ, Kociba RJ, Rampy LW, and McKenna MJ. 1988. Methylene chloride: A 2-year inhalation toxicity and oncogenicity study in rats. Fundam. Appl. Toxicol. 11:48-59.

Reitz RH. 1994. Personal communication. August 5, 1994.

Rosengren LE, Kjellstrand P, Aurell A, and Haglid KG. 1986. Irreversible effects of dichloromethane on the brain after long term exposure: a quantitative study of DNA and the glial cell marker proteins S-100 and GFA. Br. J. Ind. Med. 43:291-299.

Schwetz BA, Leong KJ, and Gehring PJ. 1975. The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicol. Appl. Pharmacol. 32(1):84-96

Soden KJ, Marras G, and Amsel J. 1996. Carboxyhemoglobin levels in methylene chloride-exposed employees. J. Occup. Environ. Med. 38(4):367-371.

Stewart RD, Fisher TN, Hosko MJ, Peterson JE, Baretta ED, and Dodd HC. 1972. Experimental human exposure to methylene chloride. Arch. Env. Health 25(5):342-348.

Taskinen H, Lindbohm ML, and Hemminki K. 1986. Spontaneous abortions among women working in the pharmaceutical industry. Br. J. Ind. Med. 43:199-205.

U.S. Code of Federal Regulations (29 CFR). Final Rule for Occupational Exposure to Methylene Chloride. Federal Register 62(7):1494.

Weinstein RS, and Diamond SS. 1972. Hepatotoxicity of dichloromethane (methylene chloride) with continuous inhalation exposure at a low dose level. Proceedings of the 3rd Annual Conference on Environmental Toxicology, 25, 26, and 27 October, 1972. Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, OH.